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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/632,036	KAUMAYA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

eriod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

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1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

sposition of Claims

4)☒ Claim(s) *1,3-9,11-22 and 25-33* is/are pending in the application.

4a) Of the above claim(s) *9,11-22 and 25-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

pplication Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

iority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

achment(s)

☒ Notice of References Cited (PTO-892)

☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20010806; 20010808*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☒ Other: *IDS-20011207; Notice to Comply*.

DETAILED ACTION

1. The response to the restriction requirement filed June 7, 2004 is acknowledged and has been entered.

As explained in the Interview Summary of August 12, 2004, which was mailed August 17, 2004, Applicant's response is not considered fully responsive to the restriction and election requirement set forth in the Office action mailed August 6, 2003.

However, in order to advance prosecution, as agreed upon by the Examiner and Applicant's representative, Ms. Docherty, a new restriction and election requirement has been set forth herein, which was communicated to Ms. Docherty during the discussion of August 12, 2004.

During the discussion, Applicant provisionally elected with traverse the invention of Group I, claims 1, 3-8, and 31, and the species of invention, wherein said composition comprises a chimeric peptide comprising the HER-2 B cell epitopes of SEQ ID NO: 6 and SEQ ID NO: 42. Furthermore, Applicant elected SEQ ID NO: 17 as the species of T helper epitope to which the claims of the elected group of inventions will initially be drawn during search and examination on the merits.

The restriction and election requirement set forth in the Office action mailed August 6, 2003 is vacated.

2. Claims 1, 3-9, 11-22, and 25-33 are pending in the application. Claims 9, 11-22, and 25-33 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species of invention, there being no allowable generic or linking claim.

3. Claims 1 and 3-8 are currently under prosecution.

Election/Restrictions

4. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1, 3-8, and 31, drawn to a composition comprising a chimeric peptide, wherein said chimeric peptide comprises one or more HER-2 B cell epitopes, a T helper epitope, and a linker, wherein said HER-2 B cell epitopes are selected from the group consisting those set forth as SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 42, classified in class 530, subclass 300 or subclass 350.

Group II. Claims 9 and 11-20, drawn to a composition comprising a chimeric peptide, wherein said chimeric peptide comprises one or more HER-2 CTL cell epitopes, a T helper epitope, and a linker, wherein said HER-2 CTL cell epitopes are selected from the group consisting those set forth as SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, classified in class 530, subclass 300 or subclass 350.

Group III. Claims 21, 22, 25-29, 32, and 33, drawn to a method for stimulating an immune response in a subject, or for treating cancer in a subject, comprising administering to the subject one or a mixture of more than one chimeric peptides, which comprises one or more HER-2 B cell epitopes, and/or one or more HER-2 CTL epitopes, a T helper epitope, and a linker, wherein said HER-2 B cell epitopes are selected from the group consisting those set forth as SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 42, and wherein said HER-2 CTL epitopes are selected from those set forth as

SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, classified in class 424, subclass 185.1.

Group IV. Claim 30, drawn to a polynucleotide encoding a chimeric peptide, wherein said chimeric peptide comprises four or more HER-2 CTL epitopes, a T helper epitope, and a linker, wherein said four or more CTL epitopes are selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, classified in class 536, subclass 23.4.

5. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I, II, and IV are patentably distinct products for the following reasons:

The inventions of Groups I and II are patentably distinct from each other, since the inventions of Groups I are composition comprising a chimeric peptide comprising one or more HER-2 **B cell** epitopes, whereas the inventions of Group II are composition comprising chimeric peptides comprising one or more HER-2 **CTL** epitopes. Accordingly, if administered to an animal, the compositions would stimulate different arms of the immune system; the inventions of Group I would stimulate a humoral immune response, whereas the inventions of Group II would stimulate a cellular immune response. An antigen-specific humoral immune response is antibody-mediated; whereas an antigen-specific cellular immune response is generally mediated by cytotoxic T lymphocytes (CTL). Compositions and methods for stimulating the different arms of the immune system have acquired a separate status in the art, since, for example, depending upon the application and the objective sought, one arm of the

immune system, rather than the other, or both, is selectively targeted by suitable compositions. In general, eliciting an antigen-specific humoral immune response is achieved by an immunization with MHC class II restricted epitope (i.e., a peptide epitope that binds to a MHC class II molecule for presentation to CD4+ T cells), whereas eliciting an antigen-specific cellular immune response is generally achieved by immunizing with a MHC class I restricted epitope (i.e., a peptide epitope that binds a MHC class I molecule for presentation to CD8+ T cells). In addition, the inventions of Groups I and II are patentably distinct compositions of matter comprising distinct chimeric peptides comprising distinct amino acid sequences, since the amino acid sequences of the B cell epitopes are distinct from the amino acid sequences of the CTL epitopes, and vice versa. Therefore, the search and considerations necessary in examining the merit of claims of Group I would not suffice to provide adequate information regarding the merit of the claims of Group II, since the searches are not the same, nor is one coextensive with the other. Because different searches would have to be performed to examine the inventions of Groups I and II, an examination of both would constitute a serious burden. Since the inventions of Groups I and II are patentably distinct from the other and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

Inventions of Groups I and II and the inventions of Group IV are patentably distinct, because the inventions of Groups I and II are composition comprising chimeric peptides, whereas the inventions of Group IV are polynucleotides. Polypeptides or peptides and polynucleotides or oligonucleotides are chemically distinct products, since polypeptides and peptides are composed of polymers of amino acids, whereas polynucleotides and oligonucleotides are composed of polymers of nucleotides. Any relationship between a polynucleotide and a polypeptide is dependent upon the information provided by the nucleotide sequence of the polynucleotide, as it corresponds to an "open reading frame" encoding the amino acid sequence of the polypeptide. However, a polypeptide can be produced by means, other than the recombinant means by which a polynucleotide encoding a polypeptide might be used to

produce the polypeptide, since a polypeptide can be produced by biochemical means, including, for example, affinity chromatography. In addition, while the polynucleotide might encode the polypeptide, generally, it can also encode another polypeptide using the information provided by an alternative open reading frame; and furthermore, since a polynucleotide can be used as a probe in hybridization-based analyses, the information provided by a polynucleotide can be used isolate different polynucleotides encoding polypeptides, which have amino acid sequences that differ from the amino acid sequence encoded by the disclosed polynucleotide. Consequently, the disclosed relationship between a polynucleotide capable of encoding a polypeptide and the polypeptide is not exclusive, since either the clamed polynucleotide or the claimed polypeptide can also be related to other polynucleotides or polypeptides, which are materially and chemically different from the claimed inventions. Therefore, the search and considerations necessary in examining the merit of claims of Groups I and II would not suffice to provide adequate information regarding the merit of the claims of Group IV, since the searches are not the same, nor is one coextensive with the other. The search performed in examining claims drawn to a polynucleotide is a different from the search performed in examining claims drawn to a polypeptide. Because different searches would have to be performed to examine the inventions of Groups I or II and the inventions of Group IV, an examination of both would constitute a serious burden. Moreover, because the disclosed relationship between the polynucleotide and the polypeptide encoded by the polynucleotide is not absolute or exclusive of other relationships with different polynucleotides or polypeptides, the search of Groups I or II and the search of Group IV will likely provide information that is relevant to one but not the other group of inventions, and vice versa; and as such, searching one in addition to the other would be burdensome. Since the inventions of Groups I or II and the inventions of Group IV are patentably distinct from the other and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

Inventions of Groups I and II and the inventions of Group III are related as product and process of use. The inventions can be shown to be distinct if either or both

of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed, namely a composition comprising a chimeric peptide comprising one or more B cell epitopes and/or one or more CTL epitopes, a linker and a T helper epitope can be used in a materially different process of using that product, such as the process of using the product to purify an antibodies that bind the chimeric peptide by affinity chromatography.

The inventions of Group IV and the inventions of Group III are unrelated because the products of Group IV are not specifically used or otherwise involved in the processes of Group III.

6. Because these inventions are distinct for the reasons given above and also because the search required for any one group is not required for any other group and/or the inventions have acquired a separate status in the art as shown by their different classification or their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. This application contains claims 1, 3-8, and 31 of Group I, which are directed to patentably distinct species of the claimed invention, wherein said composition comprises a chimeric peptide comprising one or more HER-2 B cell epitopes selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 42. See MPEP § 809.

Each species of composition comprising a chimeric peptide comprising one or more HER-2 B cell epitopes is distinct from the others comprising a chimeric peptide comprising one or more different epitopes, since each epitope is a distinct peptide having an amino acid sequence that differs from the others. Accordingly, the examination of each species of composition comprising a chimeric peptide comprising one or more HER-2 B cell epitopes would require a unique search that is not required

for examination of any of the other species of composition comprising a chimeric peptide comprising one or more different epitopes, because the search of any one chimeric peptide, or any one epitope will not provide adequate information regarding any other chimeric peptide or epitope, and moreover the search of any one chimeric peptide comprising any one combination of epitopes will not provide adequate information regarding a different chimeric peptide.

Applicant is required under 35 U.S.C. 121 to specifically elect a single species of invention by identifying the one or more HER-2 B cell epitopes of which the chimeric peptide of the claimed species of composition is comprised, which species of invention will be considered for prosecution on the merits and to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner notes that the presence of one novel and nonobvious HER-2 B cell epitope contained within a chimeric peptide within a specifically claimed species of composition would render the species of invention allowable over the prior art (but not necessarily over 35 U.S.C. 101 and 112).

8. This application contains claims 9 and 11-20 of Group II, which are directed to patentably distinct species of the claimed invention, wherein said composition comprises a chimeric peptide comprising one or more HER-2 CTL epitopes selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41. See MPEP § 809.

Each species of composition comprising a chimeric peptide comprising one or more HER-2 CTL epitopes is distinct from the others comprising a chimeric peptide comprising one or more different epitopes, since each epitope is a distinct peptide having an amino acid sequence that differs from the others. Accordingly, the examination of each species of composition comprising a chimeric peptide comprising one or more HER-2 CTL epitopes would require a unique search that is not required for

examination of any of the other species of composition comprising a chimeric peptide comprising one or more different epitopes, because the search of any one chimeric peptide, or any one epitope will not provide adequate information regarding any other chimeric peptide or epitope, and moreover the search of any one chimeric peptide comprising any one combination of epitopes will not provide adequate information regarding a different chimeric peptide.

Applicant is required under 35 U.S.C. 121 to specifically elect a single species of invention by identifying the one or more HER-2 CTL epitopes of which the chimeric peptide of the claimed species of composition is comprised, which species of invention will be considered for prosecution on the merits and to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner notes that the presence of one novel and nonobvious HER-2 CTL epitope contained within a chimeric peptide within a specifically claimed species of composition would render the species of invention allowable over the prior art (but not necessarily over 35 U.S.C. 101 and 112).

9. This application contains claims 21, 22, 25-29, 32, and 33 of Group III, which are directed to patentably distinct species of the claimed invention, wherein said method comprises administering one or a mixture of more than one a chimeric peptides comprising one or more HER-2 B cell epitopes selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 42 and/or one or more HER-2 CTL epitopes selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41. See MPEP § 809.

Each species of invention comprising administering one or more chimeric peptides comprising one or more HER-2 B cell epitopes and/or one or more HER-2 CTL epitopes is distinct from the others comprising administering one or more different

chimeric peptides comprising one or more different epitopes, since each epitope is a distinct peptide having an amino acid sequence that differs from the others. Accordingly, the examination of each species of invention comprising administering a chimeric peptide or a mixture of chimeric peptides comprising one or more HER-2 B cell epitopes and/or one or more HER-2 CTL epitopes would require a unique search that is not required for examination of any of the other species of invention comprising administering a different chimeric peptide or mixture of chimeric peptides comprising one or more different epitopes, because the search of any one chimeric peptide, or any one epitope will not provide adequate information regarding any other chimeric peptide or epitope, and moreover the search of any one chimeric peptide comprising any one combination of epitopes will not provide adequate information regarding a different chimeric peptide.

Applicant is required under 35 U.S.C. 121 to specifically elect a single species of invention by identifying the one or more chimeric peptides comprising the one or more HER-2 B cell epitopes and/or the one or more HER-2 CTL epitopes which is administered, which species of invention will be considered for prosecution on the merits and to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner notes that the presence of one novel and nonobvious chimeric peptide comprising one or more HER-2 B cell epitope and one or more CTL epitopes contained within a mixture administered would render the species of invention allowable over the prior art (but not necessarily over 35 U.S.C. 101 and 112).

10. This application contains claim 30 of Group IV, which are directed to patentably distinct species of the claimed invention, wherein said polynucelotide encodes a chimeric peptide comprising four or more HER-2 CTL epitopes selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41. See MPEP § 809.

Each species of polynucletoide comprising a nucleotide sequence encoding a chimeric peptide comprising four or more HER-2 CTL epitopes is distinct from the others comprising a nucleotide sequence encoding a chimeric peptide comprising one or more different epitopes, since each epitope is a distinct peptide having an amino acid sequence that differs from the others. Accordingly, the examination of each species of polynucleotide comprising a nucleotide sequence encoding a chimeric peptide comprising one or more HER-2 CTL epitopes would require a unique search that is not required for examination of any of the other species of polynucleotide comprising a nucleotide sequence encoding a chimeric peptide comprising one or more different epitopes, because the search of any one polynucleotide comprising a nucleotide sequence encoding chimeric peptide, or any one epitope will not provide adequate information regarding any other polynucleotide comprising a nucleotide sequence encoding a chimeric peptide or epitope, and moreover the search of any one polynucleotide comprising a nucleotide sequence encoding a chimeric peptide comprising any one combination of epitopes will not provide adequate information regarding a polynucleotide comprising a nucleotide sequence encoding different chimeric peptide.

Applicant is required under 35 U.S.C. 121 to specifically elect a single species of invention by identifying the four or more HER-2 CTL epitopes of which the chimeric peptide encoded by the claimed species of polynucleotide is comprised, which species of invention will be considered for prosecution on the merits and to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner notes that the presence of one novel and nonobvious HER-2 CTL epitope contained within a chimeric peptide encoded by a claimed species of polynucleotide would render the species of invention allowable over the prior art (but not necessarily over 35 U.S.C. 101 and 112).

11. Regarding each of the requirements to elect a species of invention set forth in sections 7-10 above, Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a

listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species, which are written in dependent form, or otherwise, include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should Applicant traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103(a) of the other invention.

12. Claims 1, 3-9, 11-22, and 25-33 are further subject to the following restrictions of patentably distinct species of invention. See MPEP § 803.02.

Claims 1, 3-9, 11-22, and 25-33 are generic to a plurality of disclosed patentably distinct species of invention wherein said T helper epitope is selected from those set forth as SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 18. Applicants are required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Claim 25 is generic to a plurality of disclosed patentably distinct species of invention wherein said cancer is selected from the group consisting of breast cancer, ovarian cancer, lung cancer, prostate cancer, and colon cancer. Applicants are required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Claim 25 is generic to a plurality of disclosed patentably distinct species of invention wherein said vehicle is selected from the group consisting of an emulsion and

a microsphere or nanosphere. Applicants are required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Claim 27 is generic to a plurality of disclosed patentably distinct species of invention wherein said oil is selected from the group consisting of squalene and squalane. Applicants are required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Regarding any of the above requirements for an election of a patentably distinct species, should Applicant traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

13. During a telephone conversation with Pamela A. Docherty on August 12, 2004, a provisional election was made with traverse to prosecute the invention of Group I, claims 1, 3-8, and 31 and the species of invention, wherein said composition comprises the HER2 B cell epitopes of SEQ ID NO: 6 and SEQ ID NO: 42; see the Interview Summary mailed August 17, 2004. Furthermore, Applicant elected the species of composition comprising the T helper epitope of SEQ ID NO: 17. Affirmation of this election must be made by Applicant in replying to this Office action. Claims 9, 11-22, 25-30, 32, and 33 have been withdrawn from further consideration by the Examiner pursuant to 37 CFR § 1.142(b), as being drawn to a non-elected invention. Only claims 1 and 3-8 read on the elected species of invention. Accordingly, claim 31 has been withdrawn from further consideration by the Examiner, as being drawn to a nonelected species of invention, since claim 31 is drawn to the specie of invention wherein said composition comprises the HER2 B cell epitopes of SEQ ID NO: 6, SEQ ID NO: 9, and SEQ ID NO: 42.

14. Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

15. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

16. The requirement to elect a species of T helper epitope, which is set forth above in section 12, is withdrawn.

Information Disclosure Statement

17. The information disclosures filed August 3, 2001, August 6, 2001, and November 29, 2001 have been considered. An initialed copy of each is enclosed.

Drawings

18. The drawing set forth as Figure 5 is objected to because of the improper demarcation of the trademark Herceptin™. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Appropriate correction is required.

19. The drawing set forth as Figure 8 is objected to because the drawing is not of sufficient quality to permit its consideration.

Appropriate correction is required.

Specification

20. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences

appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequence "GPSL" depicted in the specification at page 30 (line 11), page 31 (line 6; and line 2 of the legend of Table 4), and page 32 (line 4) is not identified by the sequence identification number, SEQ ID NO: 20.

Applicant must provide appropriate amendments to the specification, inserting the required sequence identifiers.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required.

21. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include Vydac™ (page 19, line 25), Celite™ (page 20, line 18), and Slide-a-lyzer™ (page 20, line 30, through page 21, line 1).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

22. The disclosure is objected to because of the following informalities:

(a) At page 17, lines 31, "current" is misspelled as "cuurent". Appropriate correction is required.

(b) At page 27, line 9, the number of the figure to which the disclosure refers has been omitted. Appropriate correction is required.

(c) At page 32, lines 4, a typed space between "linker" and "(MVFDN4)" has been omitted. Appropriate correction is required.

(d) At page 34, lines 26, a typed space between "medium" and "(Biowhittaker)" has been omitted. Appropriate correction is required.

Claim Objections

23. Claims 6-8 are objected to because claim 6 recites, "wherein said 2 or more HER-2 B cell epitopes are different" without explicitly reciting that each of said 2 or more HER-2 B cell epitopes are different from the others. Appropriate correction is required.

Claim Rejections - 35 USC § 112

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 3-8 are directed to a genus of "functional equivalents" of SEQ ID NO: 6 or SEQ ID NO: 42, which are amino acid sequences of which a HER-2 B cell epitope is comprised.

The specification teaches "functional equivalents" of the HER-2 B cell epitopes "have the ability to induce production of antibodies which are immunoreactive with the extracellular domain of the HER-2 protein" (page 3, lines 29-31).

SEQ ID NO: 6 and SEQ ID NO: 42 are thus functional equivalents of one another, since peptides comprising both are capable of eliciting the production of antibodies that bind the extracellular domain of HER-2. Furthermore, the specification teaches other HER-2 B cell epitopes, which also have the ability to produce antibodies that bind to the extracellular domain of HER-2 (e.g., the epitope comprising SEQ ID NO: 4 or SEQ ID NO: 5); see, e.g., page 3, lines 12-31. Therefore, these other HER-2 B cell epitopes are also functional equivalents of SEQ ID NO: 6 and SEQ ID NO: 42.

However, SEQ ID NO: 6 and SEQ ID NO: 42 bear no immediately apparent, substantial structural similarity; moreover, the sequences share no common structural attribute, which in particular correlates with their shared ability to stimulate the production of antibodies that bind the extracellular domain of HER-2. Furthermore, the other disclosed HER-2 B cell epitopes apparently bear no common substantial structural features that correlate with their equivalent functions.

Notably, the functional equivalents of SEQ ID NO: 6 and SEQ ID NO: 42 are not limited to derivatives of SEQ ID NO: 6 and SEQ ID NO: 42, or necessarily to peptides comprising portions of the extracellular domain of HER-2. However, a functional equivalent of SEQ ID NO: 6 or SEQ ID NO: 42 can theoretically be derived from any protein, which has an antigenic determinant that is also displayed by HER-2, including, for example, its rat homolog, Neu, which is 89% homologous to HER-2.

The specification does not describe other proteins comprising amino acid sequences from which a peptide that is a functional equivalent could be derived; nor does it describe functional equivalents that are not derived from HER-2.

The claims encompass HER-2 B cell peptide epitopes that are functionally equivalent to peptides comprising SEQ ID NO: 6 or SEQ ID NO: 42: Some of these functional equivalents had yet to be discovered or are not described by the prior art; others, which are described by the prior art, share no disclosed particularly identifying structural feature that accounts for their common functionality.

Accordingly, neither SEQ ID NO: 6 nor SEQ ID NO: 42, nor any other amino acid sequence disclosed by the instant specification, is properly considered "representative", or adequately descriptive of the genus of functional equivalents of SEQ ID NO: 6 or SEQ ID NO: 42 to which the claims are directed. Moreover, because the amino acid sequences that are described vary substantially in structure, there appears no correlation between a structural feature shared by at least a substantial number of the members of the genus and their common ability to stimulate the production of antibodies that bind HER-2. Therefore, given the instant specification, the skilled artisan could not immediately recognize, envision, or distinguish the members of the genus of functional equivalents of SEQ ID NO: 6 and SEQ ID NO: 42, and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claim 3 is directed to a genus of "promiscuous" T helper cell epitopes; and claim 4 is directed to a genus of "functional equivalents" of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19.

The specification teaches SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19 are the amino acid sequence of T helper (Th) cell epitopes (page 4, lines 10-20). The prior art (e.g., Kaumaya et al. (Peptides: Design, Synthesis, and Biological Activity, Basava et al., Eds., Birkhauser: Boston, 1994) (of record; cited by Applicant), page 153 and 154) teaches these Th epitopes are "promiscuous", broadly or universally binding MHC class II molecules in a non-haplotype-resticted manner. The specification defines "promiscuous" Th epitopes as a Th epitope that "promotes release of cytokines that assist in bypassing MHC restriction" (page 4, lines 7 and 8).

SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19 are thus functional equivalents of one another, since peptides comprising any of these sequence are capable of "bypassing restriction", stimulating Th cells having different MHC class II haplotypes.

However, none of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19 bear no immediately

apparent, substantial structural similarity to any of the others. Moreover, for the most part, these Th cell epitopes are derived from entirely different proteins, which have unique structures and functions and comprise distinct amino acid sequences.

Notably, the functional equivalents of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19 are not limited to derivatives of those sequences.

The claims encompass T helper cell peptide epitopes that are functionally equivalent to peptides comprising SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, or SEQ ID NO: 19: Some of these functional equivalents had yet to be discovered or are not described by the prior art; others, which are described by the prior art, share no disclosed particularly identifying structural feature that accounts for their common functionality.

For example, Sotiriadou et al. (*Br. J. Cancer.* 2001; **85** (10): 1527-1534) teaches a HER-2 peptide epitope that is functionally equivalent to the promiscuous T helper epitopes comprising SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, or SEQ ID NO: 19; see entire document (e.g., the abstract). Given the instant description of the claimed invention, the skilled artisan could not have immediately recognized the HER-2 peptide described by Sotiriadou et al. as a functional equivalent of any or all of the peptides comprising SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, since the HER-2 peptide of Sotiriadou et al. bears no apparent substantial structural feature that is shared by the other promiscuous T helper cell epitopes, which structural feature accounts for their common or equivalent functions. Accordingly, the instant written description of the claimed invention would not have reasonably conveyed to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Moreover, none of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19 is properly considered "representative", or adequately descriptive of the genus of functional equivalents of those sequences to which the claims are directed. Because the amino acid sequences

that are described vary substantially in structure, there appears no correlation between a structural feature shared by at least a substantial number of the members of the genus and their common ability to bypass restriction, or to bind universally or at least broadly to a variety of Th cells having different MHC class II haplotypes. Because the members of the genus of promiscuous Th cells, which are functionally equivalent to any or all of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, can theoretically be derived from any protein, because the genus of proteins is so large, the genus of functional equivalents to which the claims are directed is very large. Because the members of the genus of functional equivalents can be derived from so many structurally varied proteins, the members of the genus of functional variants are structurally unrelated. Therefore, given the instant specification, the skilled artisan could not immediately recognize, envision, or distinguish at least a substantial number of the members of the genus of functional equivalents of SEQ ID NO: 6 and SEQ ID NO: 42, and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claim 6 is directed to a genus of "templates", wherein each of the B cell epitopes and T helper cell epitopes are attached to a member of this genus. Claim 7 is directed to a subgenus of "templates", which are "core β sheets".

The specification teaches a single member of the genus of "templates", which is a polypeptide, which is described as a "core β sheet", that presumably forms the secondary structure of a β-sheet and comprises a primary structure of two strands of alternating leucine and lysine residues connected by a linker; see, e.g., page 4, lines 27-29. Although this embodiment of the "template" is preferred, the claims are reasonably drawn to a chimeric peptide comprising a template, which is any material suitable for attaching the peptides comprising the B cell and T helper cell epitopes.

Again, the specification teaches only a single member of the genus of "templates", which is disclosed as a "core β sheet" and described as comprising two

strands of alternating leucine and lysine residues connected by a linker; see, e.g., page 4, lines 27-29.

The specification does not describe other "templates", including other "core β sheets", or other material suitable for making such "templates" and "core β sheets". For example, the specification does not include a description of any member of the genus of templates composed of an inorganic material suitable for attaching the peptides comprising the B cell and T cell epitopes; nor does the specification describe any one of the templates composed of the wide variety of non-peptide organic materials (e.g., sugars, lectins), which are also suitable. With particular regard to those members of the genus of templates, which are "core β sheets", the specification does not describe other polypeptides having the secondary structure of a β sheet to which the B cell and T cell epitopes can be attached.

Accordingly, given the instant written description of the claimed invention, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of templates to which the epitopes can be attached. Therefore, the written description would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a

disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

In summary, the specification provides an adequate written description of a peptide comprising SEQ ID NO: 6 and a peptide comprising SEQ ID NO: 42, but does not provide an adequate written description of the functional equivalents thereof. The specification provides an adequate written description of T helper cell epitopes, as a broad genus of peptide epitopes that bind to MHC class II molecules and stimulate T helper cells to produce cytokines, but does not provide an adequate written description of a subgenus of "promiscuous" T helper cell epitopes; nor does it provide sufficient written description of the "functional equivalents" of the T helper epitopes comprising any of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19. The specification provides an adequate written description of a polypeptide that forms a β sheet and comprises two strands of alternating leucine and lysine residues connected by a linker, which can be used as a "template" or scaffold for the attachment of multiple peptides comprising B and T cell epitopes, but does not provide an adequate written description of the genus of "templates", nor the subgenus of "core β sheets". Therefore, the instant disclosure of the claimed invention is insufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph.

26. Claims 1 and 3-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** a composition for stimulating an immune response to HER-2, wherein said composition comprises: (1) a chimeric polypeptide comprising: (i) a HER-2 B cell epitope comprising SEQ ID NO: 6 or a functional equivalent thereof, wherein said functional equivalent is a peptide comprising an amino acid sequence that is a fragment of amino acid sequence of the extracellular domain of HER-2, which is able to induce antibodies that bind said extracellular domain, (ii) a T helper epitope selected from the group consisting of the T helper cell epitopes taught by the prior art, including those of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or a functional equivalent thereof comprising the amino acid sequence LSLIKGVIVHRLEGV, as taught by the prior art, SEQ ID NO: 18, and SEQ ID NO: 19, and (iii) a linker consisting of a peptide or polypeptide, which adjoins said HER-2 B cell epitope and said T helper epitope, and (2) a chimeric polypeptide comprising: (i) a HER-2 B cell epitope comprising SEQ ID NO: 42 or a functional equivalent thereof, wherein said functional equivalent is a peptide comprising an amino acid sequence that is a fragment of amino acid sequence of the extracellular domain of HER-2, which is able to induce antibodies that bind said extracellular domain, (ii) a T helper cell epitope selected from the group consisting of the T helper cell epitopes taught by the prior art, including those of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or a functional equivalent thereof comprising the amino acid sequence LSLIKGVIVHRLEGV, as taught by the prior art, SEQ ID NO: 18, and SEQ ID NO: 19, and (iii) a peptide linker consisting of 1-15 amino acids, which adjoins said HER-2 B cell epitope and said T helper cell epitope, **does not reasonably provide enablement for making** the claimed compositions comprising: (a) chimeric peptides comprising any *functional equivalent of SEQ ID NO: 6 or SEQ ID NO: 42*, (b) chimeric peptides comprising *any promiscuous T helper cell epitope*, or (c) chimeric peptides comprising a *functional equivalent of a T helper epitope* selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 19.

Claims 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** a composition for stimulating an immune response to HER-2 protein, wherein said composition comprises a multivalent peptide comprising: (i) the HER-2 B cell epitope of SEQ ID NO: 6 or a functional equivalent thereof, wherein said functional equivalent is a peptide comprising an amino acid sequence that is a fragment of amino acid sequence of the extracellular domain of HER-2, which is able to induce antibodies that bind said extracellular domain, (ii) the HER-2 B cell epitope of SEQ ID NO: 42 or a functional equivalent thereof, wherein said functional equivalent is a peptide comprising an amino acid sequence that is a fragment of amino acid sequence of the extracellular domain of HER-2, which is able to induce antibodies that bind said extracellular domain, (iii) a T helper cell epitope selected from the group consisting of the T helper cell epitopes taught by the prior art, including those of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or a functional equivalent thereof comprising the amino acid sequence LSLIKGVIVHRLEGV, as taught by the prior art, SEQ ID NO: 18, and SEQ ID NO: 19, and (iv) a polypeptide to which each of said epitopes are connected, which polypeptide comprises two strands of alternating leucine and lysine residues connected by the linker of SEQ ID NO: 20 and forms a β sheet, **does not reasonably provide enablement for making** the claimed compositions comprising: (a) multivalent peptides comprising *any functional equivalent of SEQ ID NO: 6 or SEQ ID NO: 42*, (b) multivalent peptides comprising *any promiscuous T helper cell epitope*, (c) multivalent peptides comprising *any functional equivalent of a T helper cell epitope* selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 19, (d) multivalent peptides comprising *any type of template* adjoining the HER-2 B cell epitope and said T helper epitope, (e) multivalent peptides comprising such a template that is *any type of "core β sheet"*, or (f) multivalent peptides comprising such a template that is a "core β sheet" comprising two strands of alternating leucine and lysine residues connected by *any type of linker.*

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make, and thus use, the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed by Applicant would not be sufficient to enable the skilled artisan to make, and thus use, the claimed invention without having to first perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 1 and 3-8 are directed to a genus of "functional equivalents" of the B cell epitopes of SEQ ID NO: 6 and SEQ ID NO: 42. The specification describes a "functional equivalent" of a B cell epitope comprising amino acid sequences of SEQ ID NO: 6 or SEQ ID NO: 42 as "[having] the ability to induce production of antibodies which are immunoreactive with the extracellular domain of the HER-2 protein" (page 3, lines 29-31). Accordingly, both SEQ ID NO: 6 and SEQ ID NO: 42 are functional equivalents of the other, since peptides comprising either sequence are disclosed as capable of eliciting the production of such antibodies that bind HER-2. The specification further asserts that peptides comprising the amino acid sequences set forth as SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11 are also capable of producing antibodies that bind the extracellular domain of HER-2; see, e.g., page 3, lines 12-31. Thus, SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 9, SEQ ID NO: 10, and SEQ ID NO: 11 are also functional equivalents of SEQ ID NO: 6 and SEQ ID NO: 42.

The prior art teaches many peptides that are able to stimulate the production of antibodies that bind the extracellular domain of HER-2. For example, Woodbine (Doctoral Dissertation: "BIOLOGICAL EFFECTS OF ANTI-PEPTIDE ANTIBODIES

AGAINST THE HER-2/NEU RECEPTOR TYROSINE KINASE: IMPLICATIONS FOR THERAPY OF HUMAN BREAST CANCER", The Ohio State University, 1997) (of record; cited by Applicant) teaches four different HER-2 B cell epitopes, which effectively stimulate a humoral immune response against HER-2, eliciting the production of antibodies that bind the extracellular domain of HER-2; see entire document, e.g., page 63. As the extracellular domain of HER-2 is well known in the prior art, and because there are many examples of peptides that have been used as immunogens in producing antibodies that bind the extracellular domain of HER-2 have been described, many peptides comprising portions of the amino acid sequence of the extracellular domain of HER-2 can be envisioned, which can be easily synthesized and used as functional equivalents of peptides comprising SEQ ID NO: 6 and SEQ ID NO: 42.

However, the amount of guidance, direction, and exemplification disclosed is insufficient to enable the skilled artisan to make functional equivalents of SEQ ID NO: 6 and SEQ ID NO: 42, which are derived from naturally occurring proteins, other than HER-2, or synthesized using a knowledge of such protein's amino acid sequences, without undue experimentation, particularly since, because the genus of naturally occurring proteins is so large, the genus of such functional equivalents is presumably also large. The B cell epitopes described by the prior art, and those that are described in the instant specification, are have markedly different structures. Moreover, the B cell epitopes that are taught by the specification or the prior art comprise unique amino acid sequences and apparently share no common structural feature that is essential to their common ability to stimulate the production of antibody that binds the extracellular domain of HER-2. Therefore, unless a peptide has been knowingly derived from the extracellular domain of HER-2, the skilled artisan cannot instantly recognize or envision a peptide that is a functional equivalent of a peptide comprising SEQ ID NO: 6 or SEQ ID NO: 42. While many naturally occurring polypeptides do not comprise an amino acid sequence from which a functional equivalent of SEQ ID NO: 6 and SEQ ID NO: 42 can be derived, the specification does not teach those naturally occurring proteins that do. The amount of guidance, direction, and exemplification are thus not reasonably commensurate in scope with the breadth of the subject matter claimed.

Furthermore, given the broadest, reasonable interpretation, the claims could be directed to a functional equivalent, which is synthetic variant of SEQ ID NO: 6 or SEQ ID NO: 42 comprising a non-naturally occurring amino acid sequence. Such variants may have been altered by amino acid substitution, deletion, or insertion, but are nonetheless "functional equivalents" of SEQ ID NO: 6 or SEQ ID NO: 42.

In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature, since, for example, Bowie et al. (*Science*. 1990 Mar 16; **247** (4948): 1306-1310) teaches the skilled artisan cannot reliably predict which variants of a native protein function similarly to the native protein, and which do not, because the prediction of a protein's propensity to form a particular structure, and to subsequently infer detailed aspects of function from the predicted structure, is extremely complex; see entire document (e.g., page 1306, column 1). Furthermore, Bowie et al. teaches, while it is known that many amino acid substitutions are possible in any given protein, and proteins are surprisingly tolerant of amino acid substitutions, the positions within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited, particularly at positions where the amino acid residues have critical roles in the protein's structure and function, and these regions can tolerate only conservative substitutions, or none at all (page 1306, column 2).

However, the specification fails provide guidance and direction as to which amino acid residues of SEQ ID NO: 6 and SEQ ID NO: 42 are critical to their function, as the specification does not teach which amino acids are essential to MHC class II binding, for example. Moreover, the specification fails to teach which amino acids can be replaced, and by which other amino acids, such that the resultant variant retains the function of a peptide comprising SEQ ID NO: 6 or SEQ ID NO: 42.

Although Schirle et al. (*J. Immunol. Methods.* 2001; **257**: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC class II molecules, such as the B cell epitopes disclosed in the instant application, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo

situation" (page 11, paragraph bridging columns 1 and 2). Schirle et al. teaches that the main obstacle for the prediction of MHC class II ligands has been the differing degree of degeneration of motifs (page 5, column 1). Schirle et al. teaches that while some MHC haplotypes show a strong preference for certain related amino acids in the anchor positions, other haplotypes make the definition of primary anchor amino acids virtually impossible (page 5, column 1). Because of these predictive limitations, Schirle et al. teaches that, in most cases, epitope prediction is followed by binding studies with synthetic peptides in order to reduce the number of potential candidate peptides by discarding nonbinding peptide for the final analysis of recognition by peptide-specific T cells (page 8, column 1).

However, as Schirle et al. suggests, peptides that bind MHC class II molecules do not necessarily "pass the ultimate test", that is, the peptides do not always bind to and stimulate peptide-specific T helper cells *in vivo* and thereby stimulate a humoral immune response against the native antigen. Thus, the skilled artisan cannot reliably predict whether a peptide epitope, although correctly predicted to be capable of binding a MHC class II molecule, will effectively do so *in vivo*, so as to be functionally equivalent to a peptide comprising SEQ ID NO: 6 or SEQ ID NO: 42. Salazar et al. (*Clin. Cancer Res.* 2003 Nov 15; **9** (15): 5559-5565), for example, teaches that none of the patients immunized with a multipeptide vaccine comprising different HER-2 peptide epitopes developed antibody immunity against the native HER-2 molecule, even though the peptides were shown to bind MHC class II molecules with high affinity *in vitro* and stimulate peptide-specific immune responses *in vivo*; see entire document (e.g., the abstract). Accordingly, although the skilled artisan could design synthetic candidate functional derivatives of SEQ ID NO: 6 and SEQ ID NO: 42 using predictive computer software, the artisan still cannot reliably predict whether such candidates actually are functionally equivalent, effectively stimulating the production of antibodies that bind the full-length native protein. The preponderance of factual evidence thus suggests the skilled artisan could not make the claimed invention without having to first perform an undue amount of additional experimentation.

Claim 3 is directed to a subgenus of "promiscuous" T helper (Th) cell epitopes, which are from 14 to 22 amino acids in length. The specification teaches such Th cell epitopes comprise an amino acid sequence selected from the group of consisting of SEQ ID NO: 13 or a functional equivalent thereof, SEQ ID NO: 14 or a functional equivalent thereof, SEQ ID NO: 15 or a functional equivalent thereof, SEQ ID NO: 16 or a functional equivalent thereof, SEQ ID NO: 17 or a functional equivalent thereof, SEQ ID NO: 18 or a functional equivalent thereof, and SEQ ID NO: 19 or a functional equivalent thereof (page 4, lines 6-20). The specification defines a "promiscuous" Th cell epitope as "one which promotes release of cytokines that assist in bypassing MHC restriction" (page 4, lines 7 and 8).

The prior art teaches a large multitude of "T helper cell epitopes", which are generally restricted and bind only one haplotype of MHC class II molecule; but the prior art teaches relatively few "promiscuous" Th cell epitopes. Notably, the prior art teaches seven such promiscuous Th cell epitopes, which comprise amino acid sequences identical to those set forth as SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19; see, e.g., Kaumaya et al. (Peptides: Design, Synthesis, and Biological Activity, Basava et al., Eds., Birkhauser: Boston, 1994) (of record; cited by Applicant), page 153 and 154. In addition, the prior art teaches a functional equivalent of the Th cell epitope of SEQ ID NO: 17, which comprises the amino acid sequence LSLIKGVIVHRLEGV that is nearly identical to SEQ ID NO: 17, but for the substitution of cysteine at position 3 for glycine; see, e.g., Woodbine (cited *supra*), page 74 (Figure 8).

In general, the promiscuous Th cell epitopes described by the prior art, which included those described in the instant specification, are derived from different proteins having markedly different structures and functions (e.g., tetanus toxoid and measles virus F protein), though presumably at least a very large number of proteins comprise an amino acid sequence that could be defined as a "promiscuous" Th cell epitope. Therefore, the genus of promiscuous Th epitopes is deemed very large and very diverse.

Notably the promiscuous Th cell epitopes that are taught by the specification or the prior art comprise unique amino acid sequences, which apparently share no common structural features that is essential to their common ability to bypass haplotype restriction and induce humoral immune responses in animals of differing haplotypes by promoting the release of cytokines by Th cells. Accordingly, the different members of the genus of Th cell epitopes differ markedly in structure and bare no common structural features that correlate with their ability to function in a promiscuous, non-haplotype-specific, broadly, or universally restricted manner.

The specification provides insufficient guidance, direction, and exemplification to enable the skilled artisan to make other members of the genus of "promiscuous" Th cell epitopes, including the functional equivalents of those described by the prior art, because the specification does not teach one to make at least a substantial number of the different members of the genus of epitopes. Moreover, because the members of the genus varying structures, which do not appear to relate to their common functionality, the skilled artisan cannot immediately envision the structures of such epitopes, so as to be capable of making them. Furthermore, given any Th epitope known in the art, the skilled artisan cannot reliably predict whether the epitope is or is not a promiscuous Th cell epitope.

Even if the various different promiscuous Th cell epitopes described by the prior art comprised homologous amino acid sequences, or shared a consensus amino acid sequence, Skolnick et al. (*Trends in Biotechnology*. 2000 Jan; **18** (1): 34-39) discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Skolnick et al. teaches even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

However, again, there appears no disclosed correlation between the structure of such promiscuous epitopes and their non-haplotype-specific, unrestricted function.

Even if one were to try to predict which Th epitopes might function promiscuously, a promiscuous Th epitope can only be identified as such by empirically determining whether a Th epitope is capable bypassing haplotype restriction to bind to and stimulate diverse Th cells having different MHC class II molecules; and the need to first perform such additional experimentation would unduly burden the skilled artisan, such that the claimed invention could not be made, and thus used, in accordance with the requirements set forth under 35 USC § 112, first paragraph.

Furthermore, neither the prior art, nor the specification teaches which amino acid residues of the known promiscuous Th cell epitopes are critical to their functions. Moreover, neither teaches which other amino acids can replace such critical amino acids, so that the resultant peptide is functionally equivalent to a peptide comprising the native epitope.

Claim 4 is directed to a genus of "functional equivalents" of the known promiscuous Th cell epitopes of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19. Notably, the functional equivalents of these epitopes are not limited to derivatives of those epitopes; therefore, the genus of functional equivalents reasonably includes any peptide derived from any naturally occurring protein, or synthesized using a knowledge of any protein's amino acid sequence, which functions to stimulate Th cells in a manner equivalent to any of the promiscuous Th epitopes of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19. For the reasons addressed above, the amount of guidance, direction, and exemplification disclosed is insufficient to enable the skilled artisan to make functional equivalents of these promiscuous Th cell epitopes, which are derived from naturally occurring proteins or synthesized using a knowledge of such protein's amino acid sequences, without undue experimentation, particularly since the genus of such functional equivalents is as large as the genus of such naturally occurring proteins. The amount of guidance, direction, and exemplification are thus not reasonably commensurate in scope with the breadth of the subject matter claimed.

Moreover, given the broadest, reasonable interpretation, claim 4 is directed to a genus of chimeric peptides comprising synthetic Th cell peptide epitopes, which are functionally equivalent variants of the known promiscuous Th cell epitopes. Such variants may have been altered by amino acid substitution, deletion, or insertion, but are nonetheless "functional equivalents" of the Th epitopes of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19.

As discussed above, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature. Again, Schirle et al. (cited *supra*) teaches that although several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC class II molecules, such as the Th cell epitopes disclosed in the instant application, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2). In addition, Schirle et al. teaches reliable epitope prediction is still only available for a limited number of organisms and alleles because little or no information is available about corresponding peptide specificities for MHC molecules (page 11, column 1). Schirle et al. discloses that to date, the focus has been on characterizing and predicting the epitopes that bind HLA-DR, with only one report on predictions of HLA-DQ-restricted epitopes (page 5, column 1).

Because the recognition motifs have not been characterized for most MHC haplotypes, it follows therefore that the skilled artisan cannot reliably predict, using resources now available, whether a variant of a native epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NOP: 18, and SEQ ID NO: 19 functions equivalently to the parental, native epitope. Therefore, a universally, or even broadly promiscuous Th cell epitope can only be identified by empirical studies that measure binding of an epitope to at least a majority of different MHC class II haplotypes, and subsequently to determine if the epitope is capable of bypassing MHC restriction by stimulating an effective humoral immune response against HER-2 in most, if not all animals. Accordingly, the amount of guidance, direction, and exemplification

provided by the specification is insufficient to enable the skilled artisan to make "functional equivalents" of the Th cell epitopes of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NOP: 18, and SEQ ID NO: 19 without having to first perform an undue amount of additional experimentation.

Claim 6 is directed to a genus of "templates", wherein the B cell and T cell epitopes are adjoined to such a "template". Although the specification teaches the "linker" of the inventions is an amino acid or a peptide (page 4, line 29), and although the "template" of claim 8, which is a "core β sheet" comprising two strands of alternating leucine and lysine residues connected by a linker, is comprised of a polypeptide, given the broadest reasonable interpretation, claim 6 is directed to a "template", which is any material to which the B cell and T cell epitopes can be attached. However, the specification only provides sufficient guidance, direction, and exemplification to make a template suitable for adjoining the B cell and T cell epitopes, which is comprised of a polypeptide that forms a β sheet and comprises two strands of alternating leucine and lysine residues adjoined by a linker that is a peptide of from about 2 to about 15 amino acids in length and comprises SEQ ID NO: 20. The specification, for example, does not teach the skilled artisan to make a template that is composed of an inorganic material suitable for attaching the peptides comprising the B cell and T cell epitopes; nor does the specification provide the teachings necessary to enable the skilled artisan to make the wide variety of non-peptide organic materials (e.g., sugars, lectins), which are suitable. Kaumaya et al. (cited *supra*) teaches that to be suitable and effective, a carrier, or such a template, must allow the incorporation of stabilized conformational determinants, such as the epitopes described in the instant specification, such that those determinants mimic the shape of the sequence in the native protein (page 157). Furthermore, Kaumaya et al. teaches if this criterion is not met, simply increasing the number of epitopes will not yield antibodies of high affinity or specificity (page 157).

The skilled artisan cannot predict which materials are, or whether any given material is, suitable for use as such a template; and therefore, the specification provides an insufficient amount of guidance, direction, and exemplification to enable the skilled

artisan to physically attach the epitopes to at least a substantial number of the structurally variable members of the genus of suitable "templates". The skilled artisan would have to first perform an undue amount of additional experimentation before making the claimed invention, the nature of which is commensurate in scope with the claims, because the skilled artisan would be left to discover other suitable materials, which are usable as "templates" by determining the chemical means by which the B cell and T cell epitopes could be attached to candidate materials and whether the B cell and T cell epitopes attached thereto elicit an effective humoral immune response against HER-2.

Claim 7 is directed to a genus of templates, which are "core β sheets". However, the amount of guidance, direction, and exemplification set forth by the specification is still not be sufficient to enable the skilled artisan to make a wide variety of such templates to which the B cell and T cell epitopes can be attached to produce a multivalent chimeric peptide capable of stimulating an effective humoral immune response against HER-2, since, in particular, the skilled artisan cannot reliably predict which polypeptides can be connected to form a β sheet, which is suitable for use in making a multivalent chimeric peptide capable of such a function. The prior art, e.g., Kaumaya et al. (cited *supra*), teaches a polypeptide consisting of two polypeptide strands of alternating leucine and lysine residues connected by a peptide linker consisting of an amino acid sequence identical to SEQ ID NO: 20 forms a β sheet structure is suitable for use as a template or scaffold for the attachment of a plurality of B and T cell epitopes. Kaumaya et al. teaches this template allows the B cell and T cell epitopes to be affixed in any combination or orientation and the resultant multivalent chimeric peptides are effective in stimulating a humoral immune response against a native protein (pages 157-159).

However, neither the prior art, nor the specification, teach other polypeptides, which form β sheets, which have had demonstrable suitability in their use as a template or scaffold for the attachment of a plurality of B and T cell epitopes in the manufacture of a multivalent chimeric peptide capable of stimulating an effective humoral immune

response against a native protein. Although many different methods have been proposed for predicting the secondary structure of a polypeptide, Kyngas et al. (*Protein Engineering.* 1998; **11** (5): 345-348), for example, teaches that trying to predict the three-dimensional structure of a protein from its amino acid sequence remains one of the most challenging problems in bioscience; see entire document (e.g., the abstract). In particular, Kyngas et al. teaches that the well-known Chou-Fasman parameters used in predicting protein secondary structure is are unreliable; see, e.g., the abstract. Furthermore, with emphasis on the ability to reliably predict the propensity of a polypeptide to form a β sheet, Pal et al. (*Acta. Crystallogr. D Biol. Crystallogr.* 2000 May; 56 (Pt 5): 589-594) (entire document, e.g., the introduction) and Street et al. (*Proc. Natl. Acad. Sci. USA.* 1999 Aug 3; 96 (16): 9074-9076) (entire document, e.g., the abstract), for examples, teach although progress has been made in understanding the many factors that determine the stability of α helices, our understanding of the factors that determine β sheet stability is much less advanced. Street et al. teaches no concise theoretical description that fully explained β-sheet propensities of the naturally occurring amino acids has yet emerged from our endeavours to understand these factors; see, e.g., page 9074, column 2. The amount of guidance, direction, and exemplification fails to provide the skilled artisan with solutions to the current problems and limitations affecting the reliability of predicting whether polypeptides, which might be suitable for use as templates to which the B cell and T cell epitopes can be attached, have a propensity to form β sheets.

Claim 8 is directed to a genus of templates, which are "core β sheets" comprising two alternating strands of leucine and lysine residues connected by any of a genus of "linkers". For these same reasons that the skilled artisan cannot reliably predict which polypeptides will adopt the conformation of a β sheet, were the template further limited to a polypeptide that forms a β sheet and comprises two strands of alternating leucine and lysine residues connected by a linker, the amount of guidance, direction, and exemplification set forth by the specification would still not be sufficient to enable the skilled artisan to make a wide variety of such templates, since one skilled in the art

cannot predict which linkers (i.e., which amino acids or which peptides) can be used to connect the two strands of alternating leucine and lysine residues, such that the resultant polypeptide forms a β sheet. The prior art (e.g., Kaumaya et al., cited *supra*) teaches that a linker consisting of an amino acid sequence that is identical to SEQ ID NO: 20, which can be used to adjoin two strands of alternating leucine and lysine residues, such that the resultant product adopts the secondary conformation of a β sheet. However, other linkers, which are also suitable have not been described by the prior art, nor has the specification provided guidance and direction to enable the skilled artisan to determine which other linkers can be used, so that the claimed invention can be made, and thus used, without having to first perform an undue amount of additional experimentation to identify and characterize such linkers.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to make, and thus use, the claimed invention without a need to perform an undue amount of additional experimentation.

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 1 and 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3-5 are indefinite because claim 1 recites, "said HER-2 B cell epitope being from 15 to 40 amino acids in length". The On-Line Medical Dictionary (published at the Dept. of Medical Oncology, University of Newcastle upon Tyne), which is available on the Internet at http://cancerweb.ncl.ac.uk/omd/, defines the term "being" as "existing", but notes also that the term "was formerly used where we now use having" (© Copyright 1997-2004 – The CancerWeb Project). In the context of the claim,

therefore, the term "being" might be understood to mean "having", since one skilled in the art would not ordinarily describe an epitope as "existing" from 15 to 40 amino acids. More generally, the skilled artisan would describe an epitope as "comprising" or "consisting of" a certain length, or number of amino acids. Accordingly, the metes and bounds of the subject matter cannot be unambiguously determined, since Applicant might regard the invention as a composition comprising a chimeric peptide comprising a HER-2 B cell epitope having from 15 to 40 amino acids in its length (noting that such an epitope is not limited to a peptide of 15-40 amino acids, as "having" is "open language"), or otherwise Applicant may regard their invention as a composition comprising a chimeric peptide comprising a HER-2 B cell epitope that is, or consists of 15 to 40 amino acids over its entire length (noting that such an epitope cannot be fewer than 15 nor greater than 40 amino acids in length, as "is" or "consists of" is "closed language"). Amending claim 1 to more particularly point out and distinctly claim the subject matter that Applicant regards as the invention can obviate this ground of rejection.

Claim Rejections - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbine (Doctoral Dissertation: "BIOLOGICAL EFFECTS OF ANTI-PEPTIDE ANTIBODIES AGAINST THE HER-2/NEU RECEPTOR TYROSINE KINASE: IMPLICATIONS FOR THERAPY OF HUMAN BREAST CANCER", The Ohio State University, 1997) (of record; cited by Applicant) in view of Harwerth et al. (*British Journal of Cancer*. 1993 Dec; **68** (6): 1140-1145).

The claimed invention:

Claims 1 and 3-5 are drawn to a composition comprising a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 6, or a functional equivalent thereof, adjoined by a linker of SEQ ID NO: 20 to a T helper epitope comprising SEQ ID NO: 17, or a functional equivalent thereof, and a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 42, or a functional equivalent thereof, adjoined by a linker to a T helper epitope comprising SEQ ID NO: 17, or a functional equivalent thereof.

The primary reference teaches or suggests:

Woodbine teaches chimeric peptides that comprise: (a) either a HER-2 B cell epitope comprising SEQ ID NO: 42 or a functional equivalent of SEQ ID NO: 6, (b) a T helper cell epitope derived amino acids 288-302 of the measles virus F protein (MVF), and (c) a linker consisting of an amino acid sequence identical to SEQ ID NO: 20 (gly-pro-ser-leu), which adjoins the HER-2 B cell epitope and the T helper cell epitope to form a colinear construct; see entire document (e.g., page 63 and page 74, Figure 8). More particularly, Woodbine teaches four different chimeric peptides: "DW1MVF (Her-2 376-395)", which comprises a HER-2 B cell epitope comprising amino acids 376-395 of HER-2; "MVFDW4 (628-647)", which comprises a HER-2 B cell epitope comprising amino acids 628-647 of HER-2; "DW5MVF (115-136)", which comprises a HER-2 B cell epitope comprising amino acids 115-136 of HER-2; and "DW6MVF (410-429)", which comprises a HER-2 B cell epitope comprising amino acids 410-429 of HER-2 (page 63). Each of the chimeric peptides comprises a linker having an amino acid sequence that is identical to SEQ ID NO: 20, as disclosed by the instant application, which adjoins the HER-2 B cell epitope and a T helper cell epitope; see, e.g., page 74, Figure 8. Woodbine teaches the chimeric peptides are highly immunogenic, as evidenced by high antibody titers as early as the third week post immunization (page 83). Woodbine teaches the antibodies produced by immunizing the animals with the different chimeric peptides is immunoreactive with the extracellular domain of HER-2 by showing that the antibodies bind SKBR3 cells; see, e.g., pages 84 and 85. Woodbine teaches these antibodies bind HER-2-expressing breast cancer cells and selectively inhibit tumor cell proliferation *in vitro*; see, e.g., page iii. Moreover, Woodbine teaches the anti-peptide

antibodies produced by the immunizing animals with the chimeric peptides retarded tumor growth in a nude mouse model. Accordingly, Woodbine suggests the antibodies raised to a peptide vaccine in humans may offer an effective, selective, and less toxic system of HER-2 positive tumor management than currently available methods, particularly since such synthetic vaccines would also avoid the dangers involved in using attenuated strains of viruses or infectious biological material as carriers and provide a cost-effective method of treatment; see, e.g., page iii.

Notably, the chimeric peptide "MVFDW4 (628-647)" comprises a HER-2 B cell epitope that is identical to the HER-2 B cell epitope set forth as SEQ ID NO: 42 in the instant application; see page 77, Figure 15. Woodbine teaches the amino acid sequence of the native epitope was altered by substituting glycine for the cysteine at position 3 of the sequence (pages 77 and 78).

In addition, Woodbine teaches other HER-2 B cell epitopes, which were predicted to be among the best candidates for inclusion in a vaccine comprising chimeric peptides such as those described (pages 71-73). Among these candidates is a B cell epitope comprising amino acids 314-338 of HER-2, which is similar to but different from the B cell epitope of SEQ ID NO: 6, as set forth in the instant application (page 73). The B cell epitope of amino acids 314-338 disclosed by Woodbine differs from the B cell epitope of SEQ ID NO: 6 at position 16, where an alanine has been substituted for a cysteine.

Nevertheless, it is noted that the specification teaches "functional equivalents" of the HER-2 B cell epitopes "have the ability to induce production of antibodies which are immunoreactive with the extracellular domain of the HER-2 protein" (page 3, lines 29-31). Accordingly, although it is noted that Woodbine does not teach a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 6, Woodbine teaches chimeric peptides comprising other HER-2 B cell epitopes, which are deemed functional equivalents of such an epitope, since each of the disclosed chimeric peptides comprising a HER-2 B cell epitope have the ability to produce antibodies that bind to the extracellular domain of HER-2.

Furthermore, it is noted that the chimeric peptides of Woodbine comprise a T helper epitope comprising an amino acid sequence that is different from the amino acid sequence set forth as SEQ ID NO: 17; see, e.g., page 74, Figure 8. The third amino-terminal amino acid of SEQ ID NO: 17 is glutamic acid; whereas the amino acid at the corresponding position of the T helper epitope of Woodbine is a leucine. However, because Woodbine teaches a chimeric peptide comprising the disclosed Th cell epitope is functional, absent a showing otherwise, the Th epitope disclosed by Woodbine is deemed a functional equivalent of the Th epitope of SEQ ID NO: 17.

The primary reference does not explicitly teach or suggest:

Woodbine does not teach or explicitly suggest combining the disclosed chimeric peptides in formulating a composition for stimulating an immune response to HER-2; therefore, Woodbine does not teach or explicitly suggest the elected invention, namely a composition comprising a composition comprising a chimeric peptide according to claim 1, wherein said sequence is SEQ ID NO: 6 or a functional equivalent thereof, which further comprises a second chimeric peptide according to claim 1, wherein said sequence is SEQ ID NO: 42 or a functional equivalent thereof.

The secondary reference teaches or suggests:

Harwerth et al. teaches a combination of two monoclonal antibodies, which antibodies react with two distinct epitopes of the extracellular domain of HER-2, more effectively retarded the growth of HER-2-postive tumors in nude mouse models, as compared to either of the antibodies alone; see entire document (e.g., the abstract).

The obviousness of the claimed invention:

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have produced a composition comprising a combination the two functionally equivalent chimeric peptides comprising the B cell epitope of SEQ ID NO: 42 or a functional equivalent of the B cell epitope of SEQ ID NO: 6, as disclosed by Woodbine, because Woodbine teaches the chimeric peptides elicit antibodies reactive against different epitopes of the extracellular domain of HER-2, which bind to tumor cells expressing HER-2 to retard their growth, whereas Harwerth et al. teaches a combination of antibodies reactive against different epitopes of the extracellular domain

of HER-2, which bind to tumor cells expressing HER-2 to retard their growth, can be used more effectively than any of the antibodies alone. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to produce a composition that can be used to more effectively retard the growth of HER-2-positive tumors.

31. Claims 1, 4, and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbine DB (Doctoral Dissertation: "BIOLOGICAL EFFECTS OF ANTI-PEPTIDE ANTIBODIES AGAINST THE HER-2/NEU RECEPTOR TYROSINE KINASE: IMPLICATIONS FOR THERAPY OF HUMAN BREAST CANCER", The Ohio State University, 1997) (of record; cited by Applicant) in view of Kaumaya et al. (Peptides: Design, Synthesis, and Biological Activity, Basava et al., Eds., Birkhauser: Boston, 1994) (of record; cited by Applicant).

The claimed invention:

Claims 1, 4, and 6-8 are drawn to a composition comprising a multivalent chimeric peptide comprising the HER-2 B cell epitope of SEQ ID NO: 6, or a functional equivalent thereof, the HER-2 B cell epitope of SEQ ID NO: 42, and a T helper cell epitope selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or a functional equivalent thereof, SEQ ID NO: 18, and SEQ ID NO: 19, each of which are joined to a polypeptide linker ("template") consisting of two strands of alternating leucine and lysine residues connected by a peptide linker.

The primary reference teaches or suggests:

Woodbine teaches that which is set forth in the above rejection under 35 USC § 103(a).

Again, the specification teaches "functional equivalents" of the HER-2 B cell epitopes "have the ability to induce production of antibodies which are immunoreactive with the extracellular domain of the HER-2 protein" (page 3, liens 29-31). Accordingly, although it is noted that Woodbine does not teach a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 6, Woodbine teaches chimeric peptides

comprising other HER-2 B cell epitopes, which are deemed functional equivalents of such an epitope, since each of the disclosed chimeric peptides comprising a HER-2 B cell epitope have the ability to produce antibodies that bind to the extracellular domain of HER-2.

The primary reference does not explicitly teach or suggest:

Woodbine does not explicitly teach a multivalent chimeric peptide comprising the HER-2 B cell epitope of SEQ ID NO: 6, or a functional equivalent thereof, the HER-2 B cell epitope of SEQ ID NO: 42, and a T helper cell epitope selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or a functional equivalent thereof, SEQ ID NO: 18, and SEQ ID NO: 19, each of which are attached to a "core β sheet template" comprising two strands of alternating leucine and lysine residues connected by a linker. Moreover, Woodbine does not teach or explicitly suggest a chimeric peptide comprising more than one B cell epitope and a T cell epitope, which are each attached or linked to a common "template".

The secondary reference teaches or suggests:

Kaumaya et al. teaches multivalent B cell chimeric peptide vaccines, which comprise a plurality of the same or different B cell epitopes and a plurality of T helper cell epitopes covalently attached to either strand of a "β sheet template", which is a polypeptide comprising two strands of alternating leucine and lysine residues connected by a linker; see entire document, particularly pages 157-159 and Figure 9-7. Kaumaya et al. teaches the advantage to using the disclosed "β sheet template" to produce a multivalent chimeric peptide is that it allows multiple B- and T-cell epitopes to be linked in any combination and orientation, such that the epitopes have a stabilized conformation that mimics the shape of the sequence in the native protein (page 157). Kaumaya teaches T helper cell epitopes comprising SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, or SEQ ID NO: 19 are "promiscuous", since the epitopes function to stimulate immune responses in animals of multiple different haplotypes and are thus not haplotype-restricted, or haplotype-specific (pages 153 and 154). Kaumaya teaches the multivalent chimeric

peptides are extremely immunogenic, inducing high-titered antibodies specific for the native protein (page 158). Kaumaya et al. teaches the multivalent chimeric peptides produced enhanced immune responses in animals, as compared to those produced by colinear chimeric peptide comprising the same B cell epitope adjoined to same T helper cell epitope by a linker (page 157). Furthermore, Kaumaya et al. teaches that by grafting dual copies of the B cell epitopes onto the "template", they were able to raise antibodies in the strains of animals, which did not respond to the colinear chimeric peptide (page 158). Accordingly, Kaumaya et al. teaches the multivalent chimeric peptides are capable of bypassing haplotype restriction associated with a B cell epitope (page 158).

The obviousness of the claimed invention:

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce a multivalent chimeric peptide comprising the HER-2 B cell epitope of SEQ ID NO: 42, a functional equivalent of a HER-2 B cell epitope of SEQ ID NO: 6, and a T helper cell epitope, which is any of the promiscuous T helper epitopes taught by Kaumaya et al. or the functional equivalent of the T helper epitope of SEQ ID NO: 17 taught by Woodbine, adjoined to a polypeptide consisting of two strands of alternating leucine and lysine residues connected by a linker, as described by Kaumaya et al., because while Woodbine teaches that colinear chimeric peptides comprising the B cell and T cell epitopes adjoined by a linker elicit antibodies reactive against different epitopes of the extracellular domain of HER-2, which bind to tumor cells expressing HER-2 to retard their growth, Kaumaya et al. teaches that such a multivalent chimeric peptide is more immunogenic than the colinear chimeric peptides of Woodbine and are capable bypassing haplotype restriction associated with a B cell epitope, raising antibodies against the B cell epitope in animals of different haplotypes, which do not respond to such colinear peptides. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to produce a composition that can be used to bypass haplotype restriction to more effectively produce antibodies that retard the growth of HER-2-positive tumors.

Conclusion

32. No claims are allowed.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
October 8, 2004